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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/831,580	09/28/2001	Qingyun Liu	20332P	7013

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MERCK AND CO INC
P O BOX 2000
RAHWAY, NJ 070650907

EXAMINER	
MURPHY, JOSEPH F	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 12/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/831,580	LIU ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication app ars on th cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 September 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *10-13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *09222003* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-9 in the Paper submitted 9/22/2003 is acknowledged. The traversal is on the ground(s) that a search of the protein of Group I would of necessity include a search of Group III, drawn to an antibody. This is not found persuasive because CFR 1.475 (a) indicates that a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. Groups I and III are drawn to separate, distinct inventions and are distinguished from each other because the special technical features which define them by chemical and physical characteristics i.e. structure/function, as well as biological functions are different and these special technical features are not shared by each invention. Applicant elected the invention of Group I, Claims 1-9, drawn to a DNA encoding the protein of SEQ ID NO: 2, expression vector comprising the DNA encoding SEQ ID NO: 2, a host cell comprising the vector, and the protein of SEQ ID NO: 2. The claims of Group I were not joined with claims reciting an antibody to SEQ ID NO: 2 because the invention of Group I was found to have no special technical feature that defined the contribution over the prior art of the Stratagene Catalogue. Since these special technical features are not shared by each product and since the common features do not establish an advance over the prior art, the inventions of Groups I and III do not form a single inventive concept within the meaning of Rule 13.2.

Claims 10-13 are withdrawn from consideration pursuant to 37 CFR 1.142(b). The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

References on pages 3 and 4 of the IDS submitted 9/22/2003 have been lined through because they are not in the correct format. The citation should include the author and publication date, pursuant to 37 CFR 1.98.

Claim Objections

Claims 8-9 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 6 is drawn to a protein having the sequence of SEQ ID NO: 2, while claims 8 and 9 are drawn to protein having one or two substitutions of SEQ ID NO: 2. Since the amino acid sequences with the substitutions could be infringed without infringing the sequence of SEQ ID NO: 2 in the base claim, the claims are improperly dependent.

Claim Rejections - 35 USC §§ 101; 112 first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 3 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 3 is directed to a DNA molecule that hybridizes under stringent conditions to a DNA molecule encoding SEQ ID NO: 2. However, no conditions are set forth in

the claim. Given the indefinite nature of the claim language (see rejection under 35 USC 112 second paragraph, infra) the claim reads on DNA molecules that would be expected to be present in cells, and thus the claim reads on a product of nature. Adding a limitation wherein the DNA molecule is isolated would obviate this rejection.

Claims 1-9 are rejected under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility. The instant application has provided a description of an isolated DNA encoding a protein and the protein encoded thereby. The instant application does not disclose the biological role of this protein or its significance. The claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Novel biological molecules lack well-established utility and must undergo extensive experimentation. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

It is clear from the instant specification that the HG07 polypeptide of SEQ ID NO: 2 has been assigned a function because of its similarity to known proteins (Specification at 3, lines 26-30). The encoded polypeptide of the instant invention is alleged to be structurally analogous to a protein which is known in the art to function as a leukotriene B4 receptor. However, it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors (Doerks et al.1998). These errors can be due to sequence similarity of the query region to a region of the alleged similar protein that is not the active site, as well as homologs

that did not have the same catalytic activity because active site residues of the characterized family were not conserved (Doerks et al. page 248, column 3, fourth and fifth paragraphs). Inaccurate use of sequence-to-function methods have led to significant function-annotation errors in the sequence databases (Doerks et al. page 250, column 1, third paragraph). Furthermore, Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Additionally, even if, *arguendo*, the nucleic acid encoding the HG07 polypeptide of SEQ ID NO: 2 is found to be a G-protein coupled receptor, it is an orphan receptor. Since the ligand to this receptor is unknown, the function of the protein is also unknown. Neither the specification nor the art of record disclose any diseases or conditions associated with the function or expression of the HG07 polypeptide of SEQ ID NO: 2, therefore, there is no "real world" context of use. Further research to identify or reasonably confirm a "real world" context of use is required. In the instant case, the fact that the claimed invention encodes a GPCR is not sufficient to establish a specific and substantial utility. Although GPCRs have been found to be involved in many different processes and have been the target of much research and drug discovery, unless the specific ligand for each receptor is known, unless the biological activity of the

receptor is disclosed and unless the processes that each receptor is involved in are identified, the receptor has no "real world" use, and therefore, lacks specific and substantial utility.

The instant claims are drawn to a polynucleotide and the encoded polypeptide that has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as having an amino acid sequence as set forth in SEQ ID NO: 2, the instant invention is incomplete. In the absence of knowledge of the natural substrate or biological significance of the encoded protein disclosed in the instant application, there is no immediately obvious patentable use for it. The Specification asserts that the protein of the instant claims can be used to generate antibodies, however, this asserted utility is not substantial or specific. Such methods can be performed with any polypeptide. Further, the specification discloses nothing specific or substantial for the antibody polypeptide which is produced by this method. Since this asserted utility is not present in mature form, so that it could be readily used in a real world sense, this asserted utility is not substantial or specific. The specification further asserts that the polypeptide can be used to identify agonist or antagonists, however, since the ligand to this receptor is unknown and the function of the protein is also unknown, and given the uncertainty in predicting function from structural information alone, this asserted utility is also not present in mature form, and is not specific or substantial. The specification further asserts that the polynucleotide can be used as a chromosomal marker. However, this asserted utility is not substantial or specific. Such assays can be performed with any polynucleotide. Further, the specification does not disclose a specific DNA target. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial or specific. Since the

instant specification does not disclose a "real world" use for the polynuceltoides encoding the protein identified in the specification as having an amino acid sequence as set forth in SEQ ID NO: 2, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Claims 1-9 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Assuming, arguendo, that a patentable utility is found for the polynucleotide encoding SEQ ID NO: 2, or the polypeptide of SEQ ID NO: 2, claims 3, 8-9 would be rejected under 35 U.S.C. 112, first paragraph, because the specification, which would be enabling for a full length polypeptide of SEQID NO: 2, or the polynucleotide encoding a full-length polypeptide of SEQ ID NO: 2, does not reasonably provide enablement for a DNA sequence which hybridizes to a nucleic acid encoding SEQ ID NO: 2, or a polypeptide containing mutations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a DNA molecule which hybridizes to the polynucleotide encoding SEQ ID NO: 2, and to variants of the polypeptide of SEQ ID NO: 2, thus the claims are thus directed to variant polypeptides. Claims 3, 8-9 are overly broad since insufficient guidance is provided as to which of the myriad of variant polypeptides and variant encoded polypeptides will retain the characteristics of the polypeptide of SEQ ID NO: 2. Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible

variants of the encoded SEQ ID NO: 2. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, as an example of the unpredictable effects of mutations on protein function, Mickle et al. teaches that cystic fibrosis is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (CFTR) (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation a glycine replaces the aspartic acid at position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving ride to the CF phenotype. Thus showing that even the substitution or deletion of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally, it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Since the claims encompass variant polypeptides and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is

necessary, it is undue. The claims do not set forth a functional limitation for the variant polypeptides. Since the amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of polypeptide are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polypeptides that the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed polypeptides, or polynucleotides encoding them. Applicant is required to enable one of skill in the art to make and use the claimed invention, while the claims encompass polypeptides that the specification only teaches one skilled in the art to test for functional variants. Since the claims do not enable one of skill in the art to make and use the claimed polypeptides, or polynucleotides encoding them, but only teaches how to screen for the claimed polypeptides, and since detailed information regarding the structural and functional requirements of the polypeptides, or polynucleotides encoding them are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, since Applicant has only taught how to test for polypeptide variants of SEQ ID NO: 2, or polynucleotides encoding them, and has not taught how to make polypeptide variants of SEQ ID NO: 2, or polynucleotides encoding them, it would require undue experimentation of one of skill in the art to make and use the claimed polypeptides, or polynucleotides encoding them.

Claim 3, 8-9 are rejected, under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. The claims are directed to a DNA molecule which hybridizes to the polynucleotide encoding SEQ ID NO: 2, and to variants of the polypeptide of SEQ ID NO: 2, thus the claims are thus directed to variant polypeptides. The specification and claim do not indicate what distinguishing attributes shared by the members of the genus. Thus, the scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The specification and claim do not provide any guidance as to what changes should be made. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and

because the genus is highly variant, SEQ ID NO: 2 is insufficient to describe the genus. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the genus of polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polynucleotides and polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim 5 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a host cell in culture comprising a polynucleotide with the sequence as set forth in SEQ ID NO: 1, encoding the amino acid of SEQ ID NO: 2, does not reasonably provide enablement for in vivo transfection.

The specification on page 7, lines 24 to 33 discloses that the nucleic acids of the current invention can be expressed in a wide variety of host cell types, not limited to cell lines. Thus the claims read on host cells comprising the nucleic acid within a host animal. However, there are no actual or prophetic examples that disclose how to make or use host cells that comprise a DNA sequence as set forth in SEQ ID NO: 1 in an animal. The Examiner cites Eck & Wilson (page 81, column 2, second paragraph to page 82, column 1, second paragraph) who report that numerous factors complicate *in vivo* gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. Since the instant disclosure does not address any of the methods necessary to make a host cell in an animal which comprises the polynucleotide of interest, the claims as

written are not enabled. This rejection could be overcome by addition of the limitation wherein the host cells are isolated.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 3 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 3 recites the term "stringent conditions", which is a conditional term and renders the claim indefinite. Furthermore, some nucleic acids which might hybridize under conditions of moderate stringency, for example, would fail to hybridize under conditions of high stringency. The metes and bounds of the claim thus cannot be ascertained. This rejection could be obviated by supplying specific conditions supported by the specification which Applicant considers to be "stringent".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 3 is rejected under 35 U.S.C. 102(b) as being anticipated by the Stratagene Catalogue (1991).

The Stratagene catalogue teaches the use of random 9-mers capable of hybridizing to all gene sequences. The random primers meet the limitations of claim 3 in that said primers are isolated DNA capable of hybridizing to a sequence encoding the amino acid of SEQ ID NO: 2 under the conditions provided in the claim.

Conclusion

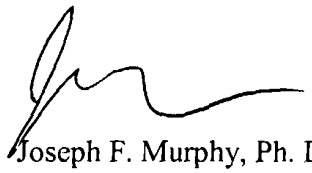
No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
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